Molecular Medicine Comes of Age

One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and combat disease.

Saving Firm A
Role: Team Coordinator

You are an experienced executive for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. Although you worked in a research lab years ago, your assignments have changed across the years. Now, you head up a small team of scientists and biostatisticians.* The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You receive an e-mail from Firm A's vice president for research. The e-mail asks your team to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you decide to call a team meeting for the next day. To prepare for the meeting, you study the relevant section of the e-mail closely.

> . . . Drug X is a bronchodilator. That is, it opens up the breathing passages in the lungs, providing relief for people who have asthma attacks. Drug X has been tested with an initial set of 270 children for its effectiveness in alleviating wheezing symptoms associated with asthma. The results were inconclusive. Some of the children showed significant improvement when they took the drug. Other children showed little or no relief.
>
> What's going on here? Can you find a pattern in the data that will help us understand how the drug is acting? To make this drug marketable, we need to define exactly when or with whom the drug is likely to be effective. If we can't, physicians will have no reason to prescribe it over another drug.

*A biostatistician is trained in biology and statistical analysis. Biostatisticians are experts in the experimental designs and statistical methods that are most helpful in conducting research in biology and medicine.

Saving Firm A
Role: Physiologist

You are an experienced physiologist* for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists and biostatisticians.** The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been reading a research report in your office. Now, your assistant calls to say that the leader of your team has called a special team meeting to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you are not surprised your team leader has called this meeting. You don't know much about the condition the drug is intended to treat. You pull out a medical textbook to learn more about it.

Asthma

Asthma is a condition in which the smooth muscle inside the bronchioles (small tubes within the lungs) contracts abnormally. This causes the victim to have difficulty breathing. Asthma occurs in 3 to 5 percent of all people at some time in their lives. It usually is caused by an allergic reaction to foreign substances in the air, for example, pollen, dust, or pet hair.

People suffering from asthma typically are treated with drugs called bronchodilators. These substances expand the bronchioles and alleviate the abnormal contractions, making breathing easier. Most bronchodilators work by binding (attaching) to and stimulating specific receptors on the cells of the smooth muscle in the lungs. This causes the muscles to relax and the bronchioles to expand.

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Saving Firm A
Role: Molecular Biologist

You are an experienced molecular biologist* who works for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists and biostatisticians.** The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

Your assistant has left you a note. It says that the leader of your team has called a special team meeting to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you are not surprised that your team leader is taking this problem so seriously. You pick up a scientific article and decide to spend the rest of the afternoon studying it.

. . . Scientists at Elvan-Ray, a pharmaceutical company that makes an important drug for treating Alzheimer disease, have reported some new research results. There are three variants of a gene called "ApoE" (pronounced A-poh-ee). The three variants are: E2, E3, and E4. The particular gene variants that a person inherits affect his or her risk of developing Alzheimer disease. They also affect his or her response to the drug. In this study, people with particuliar variants of the gene (non-E4 versions of the gene) responded very well to the drug. People with a different variant (the E4 type of the gene) eventually got worse, even though they were taking the drug.

The article includes a table showing the response to the drug based on the patients' genotype:

Response to Drug Z by Alzheimer Genotype

Genotype, Based on ApoE Type	Improvement After Administration of Drug Z			
	None	Low	Moderate	High
E2/E2[1]				X
E3/E3[2]			X	
E4/E4[1]	X			

[1] These genotypes are uncommon.
[2] This genotype is common.

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Saving Firm A
Role: Biostatistician

You are an experienced biostatistician* who works for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists and biostatisticians. The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been analyzing a new set of test results that one of those larger teams just sent you. Now, your assistant comes into your office to say that the leader of your team has called a special team meeting. The objective is to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you are not surprised that your team leader is taking this problem so seriously. You decide you'd better learn something about the problem before the meeting. Using the company's computerized database, you call up the test results on the drug and study them carefully.

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Do not discuss or circulate these data outside Firm A.

Preliminary Results of a Study of 300 Children Treated with Drug X for Wheezing Associated with Asthma

Number of Subjects and Extent of Relief After Administration of Drug X

Response to Drug X			
Sex	**Significant Relief**	**Some Relief**	**Little Relief**
female	51 = ___%	64 = ___%	35 = ___%
male	51 = ___%	64 = ___%	35 = ___%
total	102	128	70
Pet Dander in the Home#	**Significant Relief**	**Some Relief**	**Little Relief**
pets	40 = ___%	52 = ___%	28 = ___%
no pets	62 = ___%	76 = ___%	42 = ___%
total	102	128	70

#Pet dander is tiny particles of hair, skin, or feathers that can cause an allergic reaction like asthma.

Calculate the percentages and insert them where indicated in the table. To calculate a percentage, divide the number of subjects in any category by the total number of subjects in that column. Then, multiply the result by 100. For example, for the data on "pet dander in the home," 40 people exposed to pet dander at home had "significant relief," and the total number of subjects in the "significant relief" column is 102. Thus, $40 / 102 = .39 \times 100 = 39\%$ of the people had significant relief.

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Report Form for Firm A

Use this form to organize your discussion about Drug X and report your team's results. You and your teammates will have 30 minutes to complete this form. Be prepared to explain your analysis and proposed solution to the rest of the class.

1. What is the biological problem facing Firm A with respect to Drug X?

2. Describe asthma in your own words (refer to the *Team Coordinator* and *Physiologist* handouts).

3. What is Drug X designed to do for asthma sufferers (refer to the *Team Coordinator* and *Physiologist* handouts)?

4. Look at the preliminary test results (refer to the *Biostatistician* handout). Can you predict which group will be helped most or least by Drug X? For example, does the sex of an individual make a difference? Does having pets make a difference? Explain your answers.

5. What does the example of ApoE (refer to the *Molecular Biologist* handout) suggest might be happening with Drug X? Based on this example, what might Firm A investigate?

6. Firm A's vice president for research (your teacher) will provide you with some new data. What do the new data reveal about Drug X?

7. What would be an appropriate way to prescribe Drug X?

8. Has your team solved the biological problem facing the company with respect to Drug X? What new problems has it raised?

Some New Genetic Data (Firm A)

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Preliminary Results of a Study of 300 Children Treated with Drug X for Wheezing Associated with Asthma

Number of Subjects and Extent of Relief by Genotype

	Response to Drug X		
Genotype, as Indicated by Amino Acids*	**Significant Relief**	**Some Relief**	**Little Relief**
arginine/arginine	80 (78%)	20 (16%)	8 (11%)
arginine/glycine	20 (20%)	100 (82%)	24 (35%)
glycine/glycine	2 (2%)	2 (2%)	38 (54%)
total	102	122	70

*Molecular biologists have determined that a particular protein acts as a receptor for Drug X. As shown in the left-hand column, variations in the gene that encodes this receptor protein cause different amino acids to be located at position (number) 16 in the protein. There are two amino acids listed (for example, arginine / arginine) because each person has inherited two genes that encode the receptor protein.

Saving Firm B
Role: Team Coordinator

You are an experienced executive for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. Although you worked in a research lab years ago, your assignments have changed across the years. Now, you head up a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You receive an e-mail from Firm B's vice president for research with a new assignment for your team. Although one of the company's major products is still doing very well in the marketplace, the vice president wants to be sure that the company keeps its competitive edge in this area. Because of the importance of this product to the company's well-being, you decide to call a team meeting for the next day. To prepare for the meeting, you study the relevant section of the e-mail closely.

> . . . As you know, Drug Y, a treatment for cystic fibrosis, is our company's primary product. . . .
>
> I'd like your team to spend some time identifying possible new directions we could go in developing new drugs for the treatment of this disease. Much has been learned about cystic fibrosis in the last few years. Does any of this new information suggest some different approaches we could take to treating the disease? Ideally, we could develop one or two new drugs that would supplement, or even one day replace, Drug Y as our company's major product.

Saving Firm B
Role: Physiologist

You are an experienced physiologist* for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been reading a research report in your office. Now, your assistant calls to say that the leader of your team has called a special team meeting to do some brainstorming about new approaches the company could take in developing drugs for the treatment of cystic fibrosis. You know that Drug Y, your company's major product, is widely used as a treatment for this disease. Still, a lot has been learned about cystic fibrosis in the last few years. If the company is to maintain its competitive edge, it needs to keep looking for new, more effective treatments. You don't know much about cystic fibrosis, so you pull out a medical textbook to learn more about it.

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disease that affects approximately 30,000 children and young adults in the United States. CF affects tissues that produce mucus secretions, such as the airway, the gastrointestinal tract, and the ducts of the pancreas. CF causes the body to produce an abnormally thick, sticky mucus that clogs these passages. The most characteristic symptom of CF is the excessive production of mucus in the airways and lungs. This mucus provides an ideal breeding ground for many microorganisms, and CF patients have frequent airway infections that can require hospitilization and even cause death. Thick mucus also clogs the pancreatic ducts and prevents enzymes from the pancreas from reaching the intestines to help digest food.

People with CF have many symptoms. The most common are very salty sweat; frequent coughing, wheezing, and pneumonia; and an excessive appetite, but poor weight gain and slowed growth and development.

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Saving Firm B
Role: Molecular Biologist

You are an experienced molecular biologist* for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

Your assistant has left you a note. It says that the leader of your team has called a special team meeting to do some brainstorming about new approaches the company could take in developing drugs for the treatment of cystic fibrosis. You know that Drug Y, your company's major product, is widely used as a treatment for this disease. Still, if the company is to maintain its competitive edge, it needs to keep looking for new, more effective treatments. You decide to find out what the latest research says about CF, and you pick up a recent article.

. . . In 1989, researchers at the University of Michigan and at the Hospital for Sick Children in Toronto, Canada, identified the genetic defect responsible for CF. Mutations in one gene, called the cystic fibrosis transmembrane conductance regulator (CFTR) cause the body to make nonfunctional CFTR protein. The normal CFTR protein is embedded in the cell membranes of several types of cells in the body, where it acts as a "channel" that opens and closes to control the movement of chloride ions out of the cells. Depending on the specific type of CF mutation a patient has, the CTFR protein may be reduced in quantity or missing, or it may be present but not work properly . . .

As you read, you develop a flow chart of the biological effects of the most common CF mutation:

1. A person inherits two mutated genes for the CFTR protein.

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2. These mutations result in one missing amino acid in the CFTR protein that his or her cells make.

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3. The absence of this amino acid means that the CFTR protein in his or her cells does not fold into its proper shape.

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4. Most of this improperly folded CFTR protein is destroyed before it can be inserted into the cell membrane.

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5. The absence of properly functioning CFTR protein in the cell membrane leads to abnormal movement of chloride ions and water in and out of the cell.

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6. The result of this abnormal movement of chloride ions and water is the production of thick, sticky mucus.

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*A molecular biologist studies the structure and processes of life at the molecular level. Molecular biologists are interested in such things as the structure and function of proteins and DNA and the molecular mechanisms that regulate activities inside the cell.

Saving Firm B
Role: Physician

You are an experienced physician for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been analyzing a new set of test results that one of those larger teams just sent you. Now, your assistant comes into your office to say that the leader of your team has called a special team meeting to do some brainstorming about new approaches the company could take in developing drugs for the treatment of cystic fibrosis. You know that Drug Y, your company's major product, is widely used as a treatment for this disease. Still, a lot has been learned about cystic fibrosis in the last few years. If the company is to maintain its competitive edge, it needs to keep looking for new, more effective treatments. You decide that you will prepare for the meeting by learning more about Drug Y and also by learning about other companies' products to treat cystic fibrosis. You pull out some reference material and learn that improvements in treatment across the past few years have increased the average survival time of patients with CF from under 5 years to approximately 30 years. You create a table to help you organize what you learn about these treatments, but leave the last column blank in order to discuss it with your teammates.

Summary of Existing Treatment Approaches for CF

Major Type	Description	Primary Benefit	Treatment Addresses Symptoms or Cause?
chest physical therapy	vigorous tapping on the back and chest with cupped hands	dislodges mucus from lungs, allowing better breathing and reducing the risk of infection	
antibiotics	antibiotics administered intravenously, through pills, or, in the case of Drug Y, as a medicated vapor that is inhaled	treats lung infections that can damage the lungs and even cause death	
enzyme supplements	supplements of pancreatic enzymes	improves digestion	
diet	enriched diet and supplements of vitamins and other nutrients	reduces malnutrition and improves growth and development	

Report Form for Firm B

Use this form to organize your discussion about Drug Y and report your team's results. You and your teammates will have 30 minutes to complete this form. Be prepared to explain your analysis and proposed solution to the rest of the class.

1. What is the problem facing Firm B with respect to Drug Y (refer to the *Team Coordinator* handout)?

2. Describe cystic fibrosis in your own words (refer to the *Physiologist* handout).

3. What have we learned in the past few years about the cause of CF (refer to the *Molecular Biologist* handout)?

4. What is Drug Y (and most other current treatments) designed to do for CF patients (refer to the *Physician* handout and discuss what goes in the last column of the table provided)?

5. Firm B's vice president for research (your teacher) will provide you with some new information. What clue does this new information provide about how Firm B might approach developing new treatments for CF?

6. What new approaches do you recommend Firm B consider as it attempts to design and develop one or more new treatments for CF?

7. Has your team solved the problem facing the company with respect to Drug Y? What new problems has it raised?

Some New Information (Firm B)

INTEROFFICE

TO: Team Investigating New Treatment Approaches for Cystic Fibrosis

FROM: Vice-President for Research, Firm B

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Do not discuss or circulate this memo outside Firm B.

I just heard from a colleague that another research team (not associated with our company) will apply soon for a patent on a new method for treating cystic fibrosis. These researchers have spent years studying exactly what goes wrong in CF cells. The new method they will propose involves using small fragments of a protein normally found in brain cells to create working chloride channels in CF cells that lack such channels. Does this offer us any clues about how we might change our treatment approach to CF? Are there any other places in the flow chart of biological effects of CF where we could intervene to correct the problems in CF cells?